Centrum pro výzkum toxických látek v prostředí

BIOMARKERS AND TOXICITY MECHANISMS

02 – MECHANISMS OVERVIEW

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Tento projekt je spolufinancován Evropským sociálním fondem a státním rozpočtem České republiky.

EVROPSKÁ UNIE esf

MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

OP Vzdělávání pro konkurenceschopnost

UNIVERSITAS MASARYKIANA BRUNENSIS

INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Different categorizations of MoA

- According to **target molecules** (next slide)
  - Mechanisms primarily targeting different
    - BIOLOGICAL MACROMOLECULES
      - i.e. PROTEINS and/or NUCLEIC ACIDS and/or PHOSPHOLIPIDS
    - SMALL BIOLOGICAL (ORGANIC) MOLECULES
      - E.g. Antioxidants or scavengers (vit.E, GSH)

- According to **INTERACTION** between toxicant/target (next slide)
  - Non-covalent interactions
    - Partitioning (v d Waals, H-bonds, hydrophobic interactions) → [1] below
    - Partitioning with **specific steric fit** → [3] below
  - Formation of covalent bonds
    - ... with proteins / DNA-RNA / P-lipids / small molecules → [2] below

- According to **"STERIC SPECIFICITY"** of the interaction
  - NON-SPECIFIC MECHANISMS
    - the interaction between the toxicant and the target occurs "generally" with any target of certain general properties (e.g. toxicant is able to bind to ANY protein having e.g. SH- group), it does not require specific steric (structural) properties of the target
      - **mechanisms [1] and [2] below**
  - SPECIFIC MECHANISMS
    - the toxicant interacts only with certain and specific structural properties (e.g. specific binding of a pesticide into the active site of enzyme acetylcholinesterase)
      - **mechanism [3]**

Target (receptor) in MoA / toxicodynamic = BIOMOLECULE

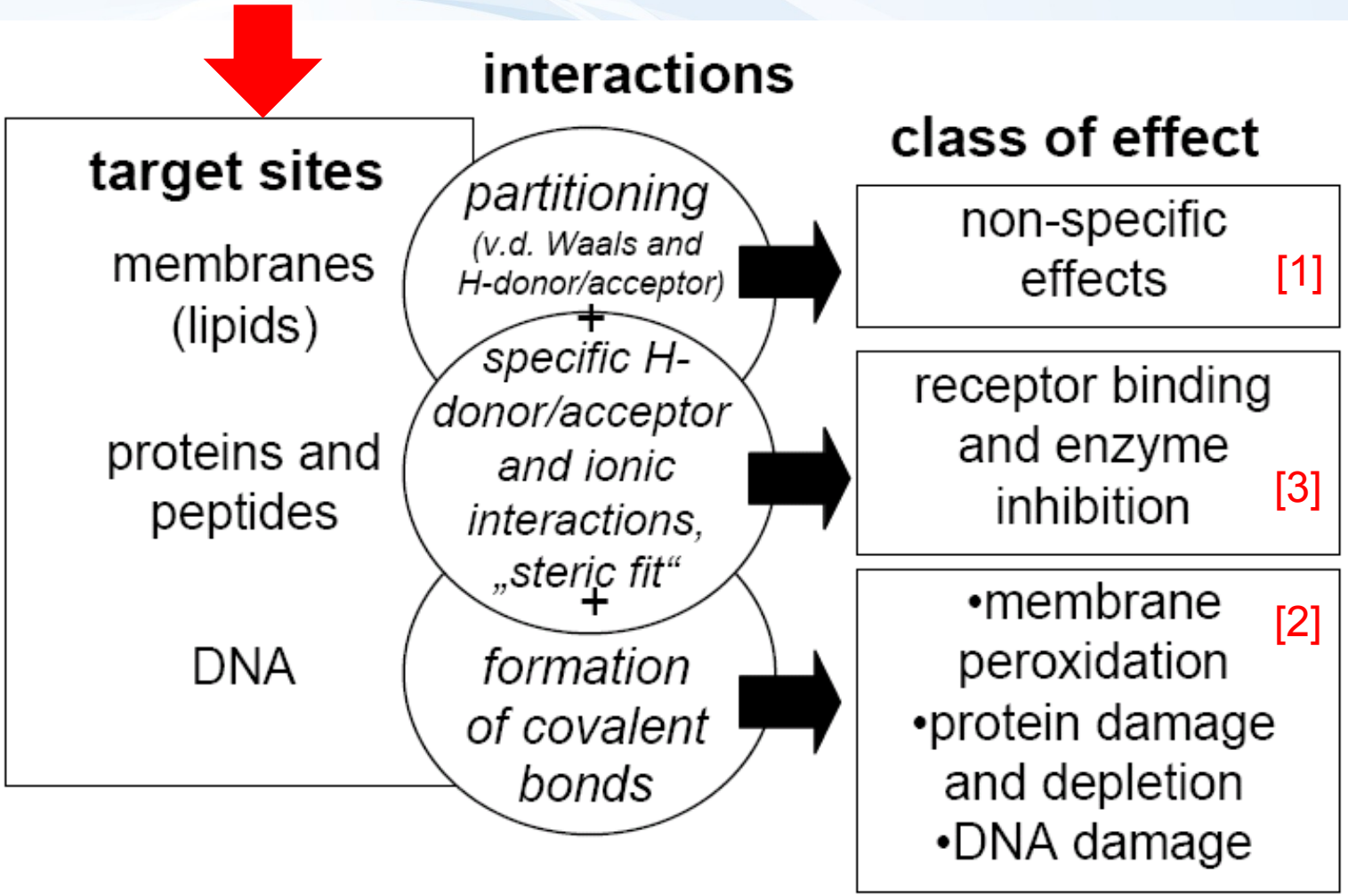


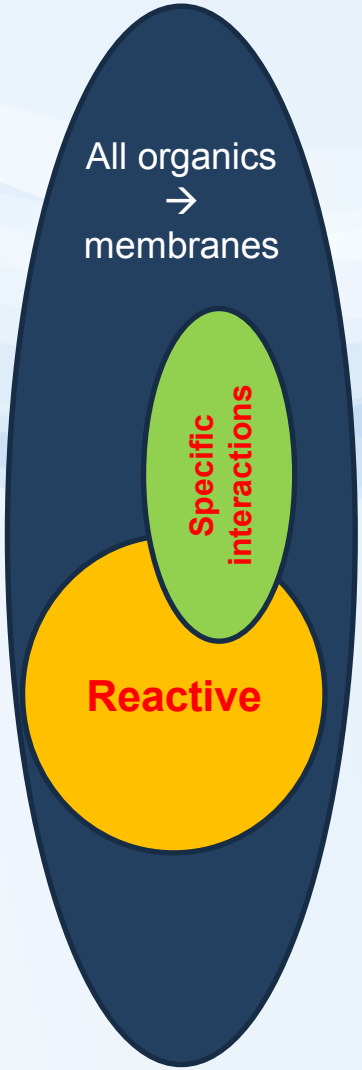
Figure 2 *Rationale behind the classification of chemicals according to mechanism: target sites and type of interaction.*

Possible categorizations of MoA

- **[1] non/specific membrane toxicity**
  - Involves ALL ORGANIC compounds
  - Affinity to non-polar environment (membrane phospholipids)
  - Two types can be discriminated
    - nonpolar basal / narcotic toxicity (
      - effects observed at relatively high concentrations, depends on hydrophobicity (Kow)
    - polar narcosis
      - more polar compounds may affect also membrane proteins (effects at lower concentrations than expected from Kow)

- **[2] nonspecific reactive toxicity**
  - some compounds with “reactive” properties may directly modify biological macromolecule (lipids, proteins, nucleic acids) causing thus toxic effects
  - reactive chemicals are mostly „electrophiles“ (reacting with „nucleophiles“ in cells – i.e. electrone-rich sites - nucleotides, -NH2, -SH and others)

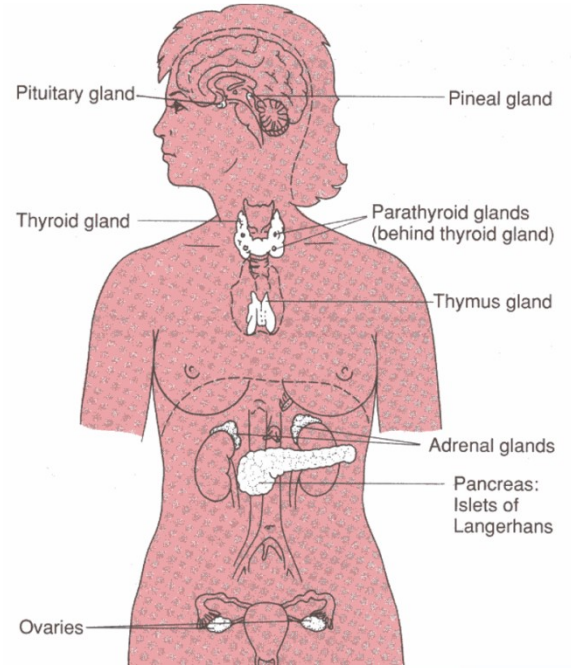
- **[3] specific steric interactions**
  - only certain specific compounds selectively affect specific targets
  - E.g. enzyme inhibitions (drugs, insecticides); receptor interactions (e.g. Estrogens)
  - Can be non-covalent as well as covalent
  - Effects at **very low** concentrations



Possible categorizations of MoA

- **Species-specific mechanisms**, examples
  - photosynthetic toxicity (only in plants) vs. teratogenicity (only in vertebrates)
  - Endocrine disruption
    - different hormonal systems in invertebrates *vs* vertebrates → different toxicity mechanisms

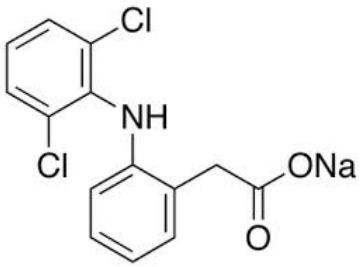
Growth in humans
several hormones

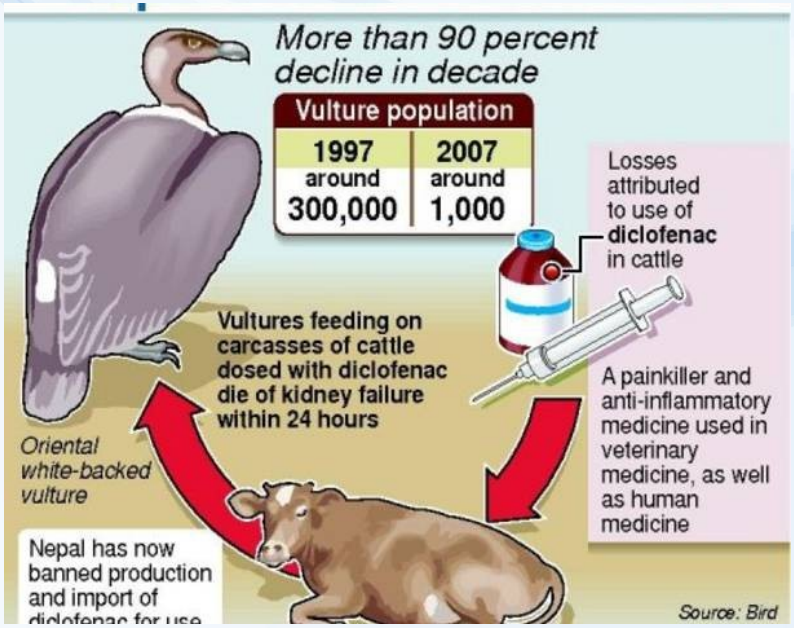


Growth in invertebrates
ecdysis (moulting) - *ecdysteroids*

Possible categorizations of MoA

- **Tissue-specific mechanisms (& effects)**
  - hepatotoxicity; neurotoxicity; **nefrotoxicity;** haematotoxicity
  - toxicity to reproduction organs;
  - immunotoxicity





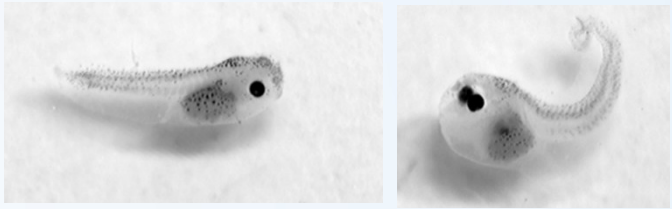
Developmental stage-specific mechanisms

- - embryotoxicity/teratogenicity: toxicity to cell differenciation processes

Thalidomide

Cyanobacterial metabolites →

Malformations in frog tadpoles



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Keywords to remember and understand

- What is it MoA?
- Can you give examples of species-specific MoA?
- What are the biological targets for toxicants? How can they be classified?
- What are the possible interactions between toxicants and biological targets?
- What is it specific and non-specific toxicity mechanism?
- What biological molecules are likely to be affected (usually at relatively high concentrations) by ALL ORGANIC COMPOUNDS?

.... and now let's look in detail on major MoAs
and their toxic consequences

Toxicity mechanisms - overview

Student is expected to know principles and some examples of the following main types of toxicity mechanisms

- **Proteins** and inhibition of enzymatic activities
- Mitotic poisons & microtubule toxicity
- Ligand competitions – receptor mediated toxicity

- **Membrane** nonspecific toxicity (narcosis)
- Toxicity to membrane gradients *(also includes proteins)*

- **DNA** toxicity (genotoxicity)

- **Complex** mechanisms
  - Oxidative stress – redox toxicity
  - Defence processes as toxicity mechanisms and biomarkers - detoxification and stress protein induction
  - Toxicity to signal transduction